Mortality Study of Pesticide Applicators and Other Employees of a Lawn Care Service Company

Shelia Hoar Zahm, ScD

In response to reports linking non-Hodgkin's lymphoma (NHL) and the herbicide 2,4-dichlorophenoxyacetic acid, a retrospective cohort mortality study of 32,600 employees of a lawn care company was conducted. The cohort was generally young with short-duration employment and follow-up. In comparison to the US population, the cohort had significantly decreased mortality from all causes of death combined (307 deaths), arteriosclerotic heart disease, and accidents. There were 45 cancer deaths (59.6 expected, standardized mortality ratio [SMR] = 0.76, 95% confidence interval [CI] = 0.55, 1.01). Bladder cancer mortality was significantly increased, but two of the three observed deaths had no direct occupational contact with pesticides. There were four deaths due to NHL (SMR = 1.14, CI = 0.31, 2.91); three were male lawn applicators (SMR = 1.63, CI = 0.33, 4.77), with two of the applicators employed for three or more years (SMR = 7.11, CI = 1.78, 28.42). No other cause of death was significantly elevated among lawn applicators as a group or among those employed for three or more years. Although based on very small numbers and perhaps due to chance, the NHL excess is consistent with several earlier studies.

From the Occupational Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Md.

Address correspondence to: Shelia Hoar Zahm, ScD, National Cancer Institute, 6130 Executive Boulevard, EPN 418, Rockville, MD 20892-7364.

1076-2752/97/3911-1055$3.00/0

Copyright © by American College of Occupational and Environmental Medicine

Pesticides are agents intended to prevent, destroy, or control insects, weeds, fungi, and other unwanted pests. They are, by design, biologically active. Many have been found to be carcinogenic in laboratory animals.[1,2] Of 47 pesticides tested in rodents by the National Cancer Institute (NCI) or the National Toxicology Program, 27 have shown evidence of carcinogenicity.[2] Evidence for the carcinogenicity of pesticides in humans, however, is limited by the small number of studies that have evaluated individual pesticides, with most studies considering pesticides as a group. The International Agency for Research on Cancer has classified only arsenical compounds as having sufficient evidence of carcinogenicity in humans and occupational exposure to insecticides as probably carcinogenic to humans.[3]

Studies of occupational groups exposed to pesticides have raised concern that pesticides may pose an important human cancer risk. Numerous studies around the world have shown that, despite their lower overall mortality, farmers experience elevated mortality from leukemia, non-Hodgkin's lymphoma (NHL), multiple myeloma, Hodgkin's disease, soft tissue sarcoma, and cancers of the skin, lip, brain, stomach, prostate, and testes.[4,5] There is evidence that pesticides may be responsible for some of these excesses, but other exposures, such as fertilizers, fuels, engine exhaust, solvents, paints, sunlight, animal viruses, and antigenic stimulation, may also play a role.[4,5]

Other occupational groups involved with pesticide application include lawn care service workers, structural pest control operators, gardeners, golf course workers, forestry workers, and right-of-way maintenance workers. Less research has been done on these groups than on farmers, but epidemiologic studies have reported excess risks of leukemia,[6] NHL,[6,7] soft tissue sarcoma,[6] and cancers of the brain,[7,8] prostate,[7] lung,[7,9,10] liver,[11] and colon.[7]

In 1986, a case-control study conducted in Kansas[12] focused attention on 2,4-dichlorophenoxyacetic acid (2,4-D), one of the most commonly used broadleaf herbicides in the United States. This compound has been used extensively in agriculture on crops such as wheat, corn, oats, rye, barley, sugarcane, and sorghum. It is also used on range and pastureland, in forestry, on rights-of-way, and on lawns and other turf. Hoar et al[12] reported a twofold excess risk of NHL among farmers who reported using phenoxy herbicides. Risk rose significantly with days per year of use of herbicides, surpassing sevenfold among those reporting use for 21 or more days per year and reporting use of 2,4-D. These results were consistent with studies from Sweden indicating a sixfold excess of malignant lymphoma among persons exposed to phenoxy herbicides or chlorophenols.[13] Since that time, NHL has been found to be elevated among farmers frequently exposed to 2,4-D or phenoxy herbicides in Nebraska,[14] Canada,[15] and Australia.[16] In New Zealand, however, duration and frequency of use of phenoxy herbicides were not associated with NHL.[17] Similarly, NHL was not significantly associated with 2,4-D use in a study conducted in Iowa and Minnesota,[18] but no information was collected on days per year of use in the original interviews. A later effort to collect intensity-of-use information suffered from the greater mortality among the cases than the controls, and the data were judged to be poor quality by peer reviewers.[19] In addition, a study in Washington State[20] revealed an elevated risk of NHL among farmers, but the excess did not appear to be related to phenoxy herbicides.[21] Cohorts of workers who manufacture 2,4-D and other phenoxy herbicides have not shown significant excesses of NHL,[22–24] but most were small cohorts that lacked sufficient statistical power to evaluate this relatively rare cause of death.[25] Soft tissue sarcoma[13,23,26–35] and prostate cancer[36] have also been linked to exposure to phenoxy herbicides or its contaminants, such as dioxin.

The association between NHL and 2,4-D reported in the Kansas study in 1986 was somewhat surprising because there was little toxicological evidence of carcinogenicity for this compound.[37] 2,4-D has been negative in the Ames assay, mouse micronuclei assay, and unscheduled DNA synthesis assay,[38] although some cytogenetic studies have reported positive results.[39–43] The carcinogenicity bioassays of 2,4-D published before 1986 were negative but are considered inadequate by current experimental standards.[44] New studies on rats and mice that were completed in 1986 and 1987 showed a high rate of brain cancer in male rats in the highest exposure group.[45,46] The Environmental Protection Agency (EPA) requested additional studies at higher doses to clarify the finding. Reports on these studies, submitted to the EPA in May 1996,[47–49] showed no evidence of carcinogenicity in rats or mice in either gender at any dose level.

In response to the Kansas study, ChemLawn Services Corporation (now TruGreen-ChemLawn of ServiceMaster Consumer Services, Memphis, TN), a national lawn care service company whose employees may be exposed to 2,4-D as many as 90–120 days per year, took several actions. The company (1) discontinued use of 2,4-D until its safety could be assured; (2) contracted for independent medical examinations of long-term employees by the University of Cincinnati;[50] (3) continued monitoring other exposures;[51–53] and (4) requested that NCI study the mortality of ChemLawn employees. NCI agreed to conduct a two-phase research effort consisting of retrospective and prospective components. The retrospective component would examine mortality patterns among the workers from the time the company was formed in 1969 to 1990. The maximum follow-up period for most workers would be relatively short for a cancer study, so continued follow-up with re-evaluation of mortality in the future was also planned. This report covers the retrospective component of this research effort.

Methods

Cohort Identification

ChemLawn was founded in 1969 with 13 employees in Ohio. By 1986, the corporation had grown to over 12,000 active employees in 46 states and three Canadian provinces. Personnel records were kept at branch offices and at corporate headquarters in Columbus, Ohio, until 1982, when branch records were also forwarded to the corporate headquarters.

Current employees were identified from a computerized personnel file established in 1986. Paper personnel records for active and former employees contained employment applications, personal data forms, change in status forms, payroll change request forms, and termination forms. Name, Social Security number, date of birth, race, gender, address, citizenship, state and number of driver's license, next-of-kin, and other variables were abstracted from the employee application and personal data form.

Because of the unknown degree of compliance of the branch offices with the 1982 request to send personnel records for all current and terminated employees to the corporate headquarters, other sources of information were identified to ensure as

TABLE 1
Number of ChemLawn Employees by Race,* Gender,† Year Hired, and Age Hired

Parameter	Number	(%)
Total	32,600	
Men	23,907	(73)
White	22,723	(70)
African-American	775	(2)
Hispanic	264	(1)
Asian	82	(<1)
Native American	63	(<1)
Women	8,693	(27)
White	8,159	(25)
African-American	367	(1)
Hispanic	109	(<1)
Asian	31	(<1)
Native American	27	(<1)
Year hired		
1969–1971	146	(<1)
1972–1974	607	(2)
1975–1977	1,886	(6)
1978–1980	3,544	(11)
1981–1983	9,455	(29)
1984–1986	16,951	(52)
Unknown	11	(<1)
Mean = 1982.7, median = 1984		
Age hired		
≤20 years	8,656	(27)
21–25 years	13,171	(40)
26–30 years	5,917	(18)
31–35 years	2,355	(7)
36–40 years	1,004	(3)
41+ years	1,145	(4)
Unknown	352	(1)
Mean = 24.7 years, median = 23 years		
Duration of employment		
<1 day	364	(1)
1 day–5.9 months	16,692	(51)
6–11.9 months	4,327	(13)
1–1.9 years	3,722	(11)
2–2.9 years	2,241	(7)
3–3.9 years	1,409	(4)
4–4.9 years	967	(3)
5–5.9 years	625	(2)
6–9.9 years	1,503	(5)
10–14.9 years	625	(2)
15+ years	125	(<1)
Mean = 1.6 years, median = 0.5 years		

* 4,454 subjects of unknown race were assumed to be white.

† Ten subjects of unknown gender were assumed to be men.

complete ascertainment of employees as possible. The corporate headquarters had always issued all paychecks and had several types of historical payroll records that could identify former employees. These records included W-2 forms from 1970–1976 for all employees sorted by branch; year-end payroll ledgers from 1979–1981 with branch, name, address, Social Security number, job classification, and other related data; quarterly payroll ledgers from 1982 by branch; and microfiche payroll ledgers from 1983–1985.

After editing and elimination of duplicate records and records for hirees who never reported to work, there were 33,771 current and former employees. Only 349 (1%) were based on payroll entries only. Based on review by the company, it appeared that many of the 349 were administrative employees, board members, etc. Although detailed job histories were not available, the company was able to indicate if the subjects had ever been employed as an applicator. Personnel records were available for the remaining 99% of the subjects. Canadian subjects (n = 1,171) were excluded because special procedures would have been needed to determine vital status, yielding a final cohort of 32,600.

There were 22,723 (70%) white non-Hispanic men, 775 (2%) African-American men, 264 (1%) Hispanic men, 145 (0.4%) other nonwhite men, 8,159 (25%) white non-Hispanic women, 367 (1%) African-American women, 109 (0.3%) Hispanic women, and 58 (0.2%) other nonwhite women (Table 1). These totals include ten subjects with unknown gender who were assumed to be men after review of name, jobs, and other information and 4,454 subjects with unknown race who were assumed to be white, based on the majority of subjects with known race being white. The mean year hired was 1982.7 and the median year hired was 1984. The average age hired was 24.7 years and median age hired was 23 years. Social Security numbers were available on all but twelve cohort members.

Vital Status Determination

The vital status of the cohort as of December 31, 1990, was determined through a variety of mechanisms. First, ChemLawn identified current employees and employees who had died while working for the company (n = 28). The cohort was compared with mortality tapes from the Social Security Administration, covering 1966-November 1991; the state of California, covering 1966–1989; and the National Death Index (NDI), covering 1979–1990.

Persons whose last date of employment was after the establishment of the NDI (January 1, 1979) and who had no record in the NDI were assumed to be alive. Persons not known to be alive after January 1, 1979, were traced through state motor vehicle administration records of drivers' licenses and credit bureaus.

As of December 31, 1990, 32,068 (98%) were found to be alive, 315 (1%) were deceased, and 217 (1%) had unknown vital status (Table 2). Requests for copies of death certificates were made to state vital records offices. If a certificate could not be found at the state of last known residence, requests were also sent to nearby states and all states of previous residence and employment. A total of 307 certificates were found. We were unable to locate certificates for eight subjects thought to be deceased. In the analyses, these subjects were assumed to be dead, with person-years accumulation ending at the presumed date of death, but they do not contribute to the analyses of specific causes of death. The cohort accumulated 250,868 person-years. Sixty-one percent of the person-years were accrued at ages under 30 and only 2% were accrued at age 50 or older. The average length of follow-up was 7.8 years and the median was 6.8 years.

The underlying and contributing causes of death on the death certificates were coded by a nosologist using the Ninth Revision of the International Classification of Diseases, according to the rules in effect at the time of death.

TABLE 2
Number of ChemLawn Employees by Occupation,* Race, and Gender

Occupation	White Men	Nonwhite Men	White Women	Nonwhite Women	Total
Applicators	17,066	733	757	20	18,576
Lawn specialists	14,937	639	587	16	16,179
Tree and shrub specialists	2,901	109	187	6	3,203
Pest control specialists	131	14	11	0	156
Specialists, not otherwise specified	79	3	8	0	90
Carpet specialists	1,545	139	36	2	1,722
Wash and fill truck area workers, mechanics	1,509	110	18	1	1,638
Labor/field helper (eg, limers, renovation helpers)	1,126	74	24	2	1,226
Telemarketers, customer service, collections	1,396	137	3,557	356	5,446
Clerical, data entry, accounting clerks	242	7	3,129	98	3,476
Warehouse, receiving and inventory clerks	335	40	12	2	389
Professionals/managers (branch level)	1,333	19	1,448	82	2,882
Professionals/managers (corporate level or not otherwise specified)	513	9	104	0	626
Technical, scientists, laboratory workers	186	2	43	2	233
Miscellaneous	240	15	11	0	266

* Subjects can contribute to multiple occupations.

Occupational Histories

ChemLawn did not maintain a sequential work history on one document for its employees. Instead, after each personnel action, one of three forms was sent to corporate headquarters to be placed in the employee's personnel records: change in status forms, payroll change request forms, and termination forms. Termination forms were also used sometimes for medical leaves and short- and long-term disabilities. In theory, a sequential occupational history could be constructed from the forms. The forms, however, were often missing or had incomplete data. In addition, there might be multiple forms for the same event. Constructing a complete, accurate occupational history for each subject was a difficult and extremely time-consuming.

Over 150,000 job change entries occurred for the 32,600 employees. Approximately 65,000 (43%) of these entries lacked a job code. The job change reason code and comment fields contained information that identified approximately 40,000 entries as terminations or rehires. The remaining 25,000 entries, however, had blank or uninformative entries, such as "change in status," "has a headache," and "name W-4." It was necessary to examine complete work histories for each subject with these blank or uninformative entries to determine if the action had been a job change, transfer, termination, rehire, or other action.

Each entry had to be sequenced correctly with an accurate job code. Incorrect or incomplete data could greatly affect the presumed duration of employment. For example, a subject with two sequential termination actions might have been rehired and had additional employment between the two dates. Many rules for evaluating these entries had to be developed. For example, when a first termination data was for a disability or a medical leave and a second action occurring shortly thereafter was a termination, it was deemed appropriate to "combine" them and assume that work stopped at the first date. For some records, however, the interval was so long that it suggested that the employee may have returned to work after the disability. In other cases, some "terminations" were actually changes from full-time to part-time status or transfers to other branches. Two sequential rehire dates suggested that an intervening termination date might have been missing from the file. Duration of employment would be grossly overestimated if the work was incorrectly assumed to be continuous. The codes required extensive editing to reconstruct a complete work history, which was essential for epidemiologic analysis.

Many records lacking a termination date had no pay raises, job changes, or other events to suggest ongoing employment. All available records, such as W-2 forms and payroll ledgers, were used to obtain as complete information as possible. Searches for termination dates were made of the yearly lists of records of terminated employees sent by the corporate personnel department to off-site storage. The lists for 1976–1983 did not have exact termination dates, but fact and year of termination could usually be established.

Termination and job change dates that were incomplete (eg, 7/10), missing, or ineligible (eg, 2/30) were edited based on the rest of the subject's occupational history. For example, if a subject had worked for three summers with "returning to school" as the reason for termination each fall but lacked a termination date for year 2, the missing month of termination would be assumed to be

September, as it was in years 1 and 3. If no other data or clues were available, the midpoint between the two known dates was used as a last resort.

There were 1,670 subjects who had been employed for less than seven days. Each record was examined individually, and subjects who were hired but never reported to work were excluded. All subjects who reported, even with extremely short durations of employment, remained in the cohort.

Table 1 presents the frequency of subjects by duration of employment through 1988 (although vital status data were available through 1990, employment histories were available only through 1988). Approximately two-thirds (66%) of the employees worked for less than one year, with 77% less than two years. The average length of employment was 1.6 years. The median length of employment, however, was much shorter at 0.5 years.

Missing job codes were determined by examining the associated job title, reason code, and comment fields for the action and by review of the rest of the subject's work history. Some codes could be determined by computerized algorithms, but most required individual manual review.

The detailed ChemLawn job codes were grouped into broad categories, crudely based on potential for exposure to pesticides and by job activities. All entries with codes TH (truck helper), SC (specialist), CL (clerical), and OT (other) required individual review to assign into the broad job categories. For example, the TH code was used for several jobs: carpet helper, carpet cleaner, lawn helper, tree and shrub helper, pesticide helper, production assistant, and truck helper. Each occurrence of the code was classified to a broad job category after review of the job title and comment fields, branch type (ie, lawn, tree and shrub, or carpet clean), and other variables for that job and for others in the subject's work history.

TABLE 3
Pesticides Commonly Used by ChemLawn

Name (Brand name)	Comment
Herbicides	
2,4-D	Extensive use, discontinued in 1986
2,4-D, dicamba, mecoprop (Killex, Trimec)	Extensive use
Benefin (Balan)	Extensive use
Bensulide (Betasan or Lescosan)	Extensive use
Cacodyclic acid	Infrequent use
DCPA (Dacthal)	Extensive use, very low level contaminant: 2,3,7,8-TCDD (0.13 ppb)
Dicamba (Banvel)	Extensive use
DSMA	Infrequent use
MCPA	
Mecoprop (MCPP)	Extensive use
MSMA	Infrequent use
Pendimethaline (Lesco Pre-M, Prowl)	Extensive use
Pronamide (Kerb)	
Proturf PTH	
2,4,5-trichloroproprionic acid (Silvex)	Very little use, discontinued 1978
Insecticides	
Acephate (Orthene)	Moderate or extensive use
Carbaryl (Sevin)	
Chlordane	Discontinued in 1976
Chlorpyrifos (Dursban)	Extensive use
Diazinon (Spectracide)	Extensive use
Isofenphos (Oftanol)	Moderate or extensive use
Lindane	Discontinued in 1981
Malathion	
Methoxychlor	
Fungicides	
Benomyl (Tersan)	Moderate use
Chlorothalinol (Daconil)	
Mancozeb	Moderate use
PCNB	Moderate use
Triadimefon (Bayleton)	
Other	
Dicofol (Kelthane)	Acaricide, moderate or extensive use
Exhalt	Sticker extender
Xylene	Solvent

The frequency of subjects ever employed in each broad occupational category is presented in Table 2. Employees can contribute to multiple categories. Seventy-four percent (n = 17,799) of men were ever employed as applicators with 15,576 in lawn care, 3,010 in tree and shrub, 145 in pest control operations, and 82 as applicators, not otherwise specified. The majority of women were employed in clerical, sales, and other administrative jobs, with only 777 (9%) ever employed as applicators.

The branch number, an important variable for linkage to pesticide use information, was missing for approximately 4,000 job entries. The information was obtained by examining each entry's branch name, the rest of the work history for that subject, the records of other subjects with the same branch name, and other methods.

Editing the occupational histories was an extremely lengthy process involving numerous computerized algorithms and manual review of tens of thousands of records. Multiple cycles were required to fully edit and compile the data. The details of the occupational histories that were the most difficult to resolve were those necessary for linking the records to the pesticide exposure information available at the branch level. The value of this editing effort will increase as the cohort is followed prospectively into the future.

Pesticide Use Information

When ChemLawn was founded, the company services were limited to lawn care. Applicators applied herbicides, fertilizers, insecticides, and fungicides. In 1976, tree and shrub services were added. Tree and shrub workers applied insecticides and fertilizers, but not herbicides. Branches provided primarily either lawn care or tree and shrub care with little crossover. Later divisions included PestFree (an indoor pest elimination service), CarpetClean, and commercial services. During these later years, the type of service provided by the branch was indicated in the last digit of the branch code.

Table 3 presents pesticides commonly used by ChemLawn. The herbicides included 2,4-D, benefin, bensulide (Betasan or Lescosan), DCPA (Dacthal), dicamba (Banvel), mecoprop (MCPP), and pendimethaline (Pre-M). Less frequently used herbicides included cacodylic acid, disodium methanearsonate (DSMA) and monosodium methanearsonate (MSMA). Insecticides used frequently included acephate (Orthene), chlorpyrifos (Dursban), diazinon (Spectracide), dicofol (Kelthane), and isofenphos (Oftanol). The fungicides benomyl, mancozeb, and pentachloronitrobenzene (PCNB) were also used often.

All pesticides used by ChemLawn branches have been purchased centrally through the corporate headquarters. Each year, agronomic programs were developed that specified the recommended pesticides and fertilizers, application rates, and dates of application by branch and lawn type (eg, sun, shade, insect infestation special treatments). ChemLawn estimates that on average each applicator services 625 customers with lawns averaging 6,500 square feet, yielding an average of 90 acres per application cycle per applicator. Descriptions of a large number of the pesticide programs were available at corporate headquarters or from staff in the branch offices. We were not able to obtain annual programs for every branch and no programs were available for any branch prior to 1973.

The programs used a variety of names for similar chemical formulations, which were standardized, collapsed, and classified using pesticide reference materials and the product label files maintained by ChemLawn.

The dates for each application cycle were indicated by "rounds." Each season consisted of four to six rounds, depending on geographic location, each round being several weeks in length. In some years, the pesticide programs specified the dates for each round. In other years, the rounds were simply numbered. We inputted the unknown dates from programs for the same location in other years.

A total of 3,535 programs for 1973–1984 were abstracted. Duplicate programs were identified and eliminated. Other apparent duplicates were actually distinct programs for slightly different program types (eg, sun and improved sun lawns) or were program revisions. In the latter case, the program with the latest date of submission was identified and retained. Twenty-six percent of the programs had missing branch codes and 9% were missing the year, the two variables necessary to link the pesticide program data to the cohort members' occupational histories. Considerable effort was expended to reconstruct branch codes. Missing data were obtained by review of branch name, program title, submission date, the format of the program page, and evaluation of the chemicals to identify program type, when possible. The pesticide programs for 1985–1988 were available on a computer data tape.

Probable exposures for the cohort members were identified by linking the subjects' work histories to the pesticide programs. Initial efforts to match the pesticide programs and the work histories were largely unsuccessful because of the large number of missing branch numbers and years in both files. Out of approximately 83,000 work history entries from 1973–1984, only 719 matched a pesticide program on both branch number and year, and only an additional 431 matched on branch number alone. Of the over 67,000 entries from 1984–1988, only 1,243 matched on both branch number and year plus 410 more on branch number alone. Overall, only 42% of the lawn service applicators had even one match by branch and year, and only 2% of the cohort had their entire work history linked to pesticide data for each entry. Extensive editing of the occupational histories and the pesticide program data to improve the matches was only marginally successful. It will be necessary to loosen the matching criteria from individual branch to city or state. The methods for characterizing the exposures when there are program differences in the branches within a city or state need to be developed.

Because of the ongoing work on methods to characterize pesticide use for larger geographical areas and because of the small number of deaths in the cohort to date, this report will use the pesticide program data in a descriptive manner only. The pesticides mentioned in the programs matching the work histories of subjects who died of selected causes of death will be presented. In the future, when more deaths have occurred and when procedures are developed to merge program data at the city or state level, the pesticide program data will be used to characterize individual exposures in more detail for nested case-control studies.

Additional pesticide exposure information was also available from some monitoring projects conducted by ChemLawn in recent years. Studies of blood cholinesterase activity and pesticide levels in urine, personal air samples, and area air samples from offices, warehouses, and production facilities reported exposures well below the permissible exposure limits established by the Occupational Safety and Health Administration, National Institute for Occupational Safety and Health, American Conference of Governmental Industrial Hygienists, or the World Health Organization/Food and Agriculture Organization.[51–54]

Company standard work practices are for the applicators to wear boots, gloves, eye protection, and an apron or other outer garment during mixing and loading. During application, gloves are worn if indicated by the pesticide label. If the label does not indicate that gloves must be worn, their use is optional.

Analysis

Person-years at risk were accumulated from date of hire to the earlier of either December 31, 1990, or the date last known to be alive. The observed number of deaths in the cohort were totalled by specific cause. The expected number of deaths were obtained by multiplying cause-specific mortality rates for the US population by the person-years at risk in the study group, adjusting for gender, race, age, and calendar time.[55]

Standardized mortality ratios (SMRs), the ratios of observed to expected numbers of death, and 95% confidence intervals (95% CIs) were obtained using the O/E program developed by the NCI.[56] The confidence intervals were calculated according to the method of Liddell.[57]

To calculate the expected numbers of death by duration of employment, person-years were allocated in the appropriate time-dependent manner, that is, to each duration category as the subject attained that length of employment. The remaining person-years to the closing date of the study are allocated to the last duration of employment category the subject attained. SMRs and 95% CIs for the duration analyses were obtained using the AMFIT procedure of EPICURE, a software package produced by HiroSoft International Corporation (Seattle, WA).[58] The 95% CIs were calculated as described in Breslow and Day.[59] Statistical power calculations were obtained using the EPITOME program.[60]

TABLE 4

Observed (OBS) and Expected (EXP) Numbers of Deaths, Standardized Mortality Ratios (SMR), and 95% Confidence Intervals (CI) for All ChemLawn Employees, 1969–1990, Adjusted by Race, Gender, Age, and Calendar Year*

Cause	OBS	EXP	SMR	95% CI
All causes of death	307	444.4	0.69	0.62, 0.77
Infective and parasitic disease	15	23.0	0.65	0.36, 1.08
All malignant neoplasms	45	59.6	0.76	0.55, 1.01
Digestive organs and peritoneum	10	9.7	1.03	0.49, 1.90
Large intestine	4	3.8	1.05	0.28, 2.68
Rectum	1	0.7	1.45	0.02, 8.07
Liver	1	0.8	1.18	0.02, 6.59
Pancreas	3	1.7	1.75	0.35, 5.12
Lung	7	10.8	0.65	0.26, 1.34
Bone	1	0.8	1.24	0.02, 6.89
Skin	1	3.6	0.28	0.00, 1.56
Breast	4	5.8	0.69	0.19, 1.76
Ovary	1	1.4	0.71	0.01, 3.97
Prostate	2	0.7	2.77	0.31, 10.00
Testis	1	1.3	0.74	0.01, 4.14
Bladder	3	0.4	7.10	1.43, 20.73
Brain and other central nervous system	3	4.0	0.75	0.15, 2.18
All lymphopoietic cancer	8	11.4	0.70	0.30, 1.39
Non-Hodgkin's lymphoma	4	3.5	1.14	0.31, 2.91
Hodgkin's disease	1	2.0	0.49	0.01, 2.75
Leukemia and aleukemia	3	5.0	0.60	0.12, 1.75
Benign neoplasms	1	1.2	0.81	0.01, 4.51
Allergic, endocrine, metab., nutritional dis.	6	10.8	0.56	0.20, 1.22
Diabetes mellitus	4	4.9	0.81	0.22, 2.08
Diseases of blood and blood-forming organs	1	1.2	0.85	0.01, 4.70
Mental, psychoneurotic, and personality dis.	3	6.8	0.44	0.09, 1.28
Diseases of nervous system and sense organs	5	7.2	0.70	0.23, 1.63
Diseases of circulatory system	37	62.1	0.60	0.42, 0.82
Arteriosclerotic heart disease, incl. CHD	17	33.1	0.51	0.30, 0.82
Vascular lesions of CNS	6	8.6	0.69	0.25, 1.51
Respiratory diseases	8	12.0	0.67	0.29, 1.32
Pneumonia	4	5.3	0.75	0.20, 1.92
Emphysema	2	0.7	2.87	0.32, 10.35
Diseases of digestive system	9	14.8	0.61	0.28, 1.15
Gastric and duodenal ulcer	1	0.5	1.88	0.02, 10.49
Cirrhosis of liver	7	9.1	0.77	0.31, 1.59
Diseases of genito-urinary system	1	2.6	0.38	0.00, 2.10
Symptoms, senility, and ill-defined conditions	2	11.0	0.18	0.02, 0.66
External causes of death	170	227.5	0.75	0.64, 0.87
Accidents	95	136.4	0.70	0.56, 0.85
Motor vehicle accidents	70	88.6	0.79	0.62, 1.00
Suicide	56	51.3	1.09	0.82, 1.42

* Metab., metabolic; Dis., diseases; incl., including; CHD, congestive heart disease; CNS, central nervous system.

Results

There were 307 deaths with known cause identified among the ChemLawn cohort. In comparison with the US general population, the cohort had significantly decreased mortality from all causes of death combined (SMR = 0.69), arteriosclerotic heart disease (SMR = 0.51), symptoms and ill-defined conditions (SMR = 0.18), and accidents (SMR = 0.70) (Table 4). There were 45 cancer deaths among the Chem-

TABLE 5

Observed (OBS) and Expected (EXP) Numbers of Deaths, Standardized Mortality Ratios (SMR), and 95% Confidence Intervals (CI) for Men Employed by ChemLawn as Applicators, 1969–1990, Adjusted by Race, Age, and Calendar Year

	All Applicators				Lawn Applicators				Tree and Shrub Applicators			
Cause	OBS	EXP	SMR	95% CI	OBS	EXP	SMR	95% CI	OBS	EXP	SMR	95% CI
All causes of death	177	269.0	0.66	0.56, 0.76	165	240.2	0.69	0.59, 0.80	14	39.9	0.35	0.19, 0.59
Infective and parasitic disease	12	16.7	0.72	0.37, 1.25	12	14.9	0.81	0.42, 1.41	1	2.6	0.39	0.01, 2.18
All malignant neoplasms	16	23.6	0.68	0.39, 1.10	13	21.2	0.61	0.33, 1.05	3	3.1	0.96	0.19, 2.81
Digestive organs and peritoneum	4	3.7	1.08	0.29, 2.75	4	3.4	1.19	0.32, 3.04	0	0.4		
Large intestine	2	1.4	1.45	0.16, 5.22	2	1.3	1.60	0.18, 5.77	0	0.2		
Liver	1	0.3	2.90	0.04, 16.16	1	0.3	3.22	0.04, 17.94	0	0.0		
Pancreas	1	0.6	1.75	0.02, 9.75	1	0.5	1.93	0.03, 10.76	0	0.1		
Lung	3	3.3	0.91	0.18, 2.66	2	3.0	0.67	0.08, 2.42	1	0.3	2.90	0.04,16.14
Skin	1	2.2	0.45	0.01, 2.51	1	2.0	0.50	0.01, 2.79	0	0.3		
Testis	1	1.1	0.94	0.01, 5.21	0	1.0			1	0.2	6.18	0.08,34.39
Brain and other central nervous system	2	2.3	0.88	0.10, 3.18	2	2.0	0.98	0.11, 3.54	0	0.3		
All lymphopoietic cancer	4	6.5	0.62	0.17, 1.58	3	5.8	0.52	0.10, 1.51	1	0.9	1.06	0.01, 5.88
Non-Hodgkin's lymphoma	3	2.1	1.46	0.29, 4.27	3	1.8	1.63	0.33, 4.77	0	0.3		
Leukemia and aleukemia	1	2.8	0.35	0.00, 1.97	0	2.5			1	0.4	2.39	0.03,13.28
Allergic, endocrine, metab., nutritional dis.	2	6.4	0.31	0.04, 1.13	1	5.7	0.17	0.00, 0.97	1	0.9	1.08	0.01, 6.02
Diabetes mellitus	1	2.5	0.40	0.01, 2.25	0	2.2			1	0.3	3.00	0.04,16.70
Diseases of blood and blood-forming organs	1	0.6	1.59	0.02, 8.84	1	0.6	1.76	0.02, 9.88	0	0.1		
Mental, psychoneurotic, and personality dis.	3	4.7	0.64	0.13, 1.87	3	4.2	0.71	0.14, 2.09	0	0.7		
Diseases of nervous system and sense organs	3	4.1	0.73	0.15, 2.14	3	3.7	0.82	0.16, 2.40	0	0.6		
Diseases of circulatory system	13	28.4	0.46	0.24, 0.78	13	25.8	0.50	0.27, 0.86	0	3.4		
Arteriosclerotic heart disease, CHD	5	14.5	0.34	0.11, 0.80	5	13.2	0.38	0.12, 0.88	0	1.6		
Vascular lesions of CNS	2	3.7	0.55	0.06, 1.98	2	3.3	0.60	0.07, 2.18	0	0.5		
Respiratory diseases	1	5.5	0.18	0.00, 1.02	0	4.9			1	0.7	1.39	0.02, 7.73
Pneumonia	1	2.9	0.34	0.00, 1.91	0	2.6			1	0.4	2.60	0.03,14.46
Diseases of digestive system	7	8.4	0.83	0.33, 1.71	7	7.6	0.92	0.37, 1.89	0	1.1		
Gastric and duodenal ulcer	1	0.3	3.88	0.05, 21.59	1	0.2	4.28	0.06, 23.81	0	0.0		
Cirrhosis of liver	5	5.4	0.93	0.30, 2.16	5	4.9	1.02	0.33, 2.39	0	0.7		
Symptoms, senility, and ill-defined conditions	2	7.2	0.28	0.03, 1.01	2	6.4	0.31	0.04, 1.13	0	1.1		
External causes of death	114	159.1	0.72	0.59, 0.86	108	141.4	0.76	0.63, 0.92	7	25.0	0.28	0.11, 0.58
Accidents	61	95.2	0.64	0.49, 0.82	58	84.5	0.69	0.52, 0.89	3	15.0	0.20	0.04, 0.58
Motor vehicle accidents	45	60.6	0.74	0.54, 0.99	42	53.7	0.78	0.56, 1.06	3	9.7	0.31	0.06, 0.90
Suicide	43	36.5	1.18	0.85, 1.59	41	32.5	1.26	0.91, 1.71	3	5.7	0.52	0.11, 1.53

Lawn employees (59.6 expected, SMR = 0.76, CI = 0.55, 1.01). Bladder cancer mortality was significantly increased, based on three deaths (0.4 expected, SMR = 7.10, CI = 1.43,20.73). No other cause of death differed significantly from the expected among the total cohort.

The mortality pattern among white men was similar to that for the entire cohort (230 observed, 345.4 expected, SMR = 0.67, CI = 0.58,0.76), with the exception of bladder cancer. Only one bladder cancer death was observed among the men (0.3 expected), which was not statistically significant. There were 20 deaths among nonwhite men (25.7 expected; SMR = 0.78, CI = 0.47,1.20), nine of which were due to external causes (13.0 expected, SMR = 0.69, CI = 0.32,1.32). Two cancer deaths (liver and pancreas) occurred among nonwhite men (1.8 expected; SMR = 1.08).

There were 57 deaths among women (73.4 expected, SMR = 0.78, CI = 0.59, 1.01; white women: 53 observed, 68.4 expected, SMR = 0.77, CI = 0.58,1.01; nonwhite women: 4 observed, 4.9 expected, SMR = 0.81, CI = 0.22,2.70). There were 18 deaths due to cancer among the women (22.4 expected, SMR = 0.80, CI = 0.48,1.22). The small numbers precluded meaningful analyses for most causes of death. Based on two observed deaths (0.1 expected), there was a significant excess of bladder cancer.

Men employed as applicators (lawn care, tree and shrub, pest control, or not specified) had significantly decreased mortality for all causes of death combined (SMR = 0.66), arteriosclerotic heart disease (SMR = 0.80), external causes (SMR = 0.72), accidents (SMR = 0.64), and motor vehicle accidents (SMR = 0.74) (Table 5). There were no significantly elevated causes of death among male applicators. Three NHL deaths were observed with 2.1 expected, yielding an SMR of 1.46 (CI = 0.29,4.27).

There were three deaths among the 777 women employed as applicators, one each due to bladder cancer, infectious disease, and suicide (data not shown). All were white women employed in lawn care.

Among men, most of the applicators had been employed in lawn care, with only 14 deaths observed (SMR = 0.35) among the more recently established tree and shrub operation (Table 5). All three NHL applicator deaths occurred among lawn applicators (1.8 expected, SMR = 1.63, CI = 0.33,4.77). No unusual mortality patterns were observed among the wash and fill truck area workers (15 observed, 21.5 expected, SMR = 0.70, CI = 0.39,1.15) or the labor and field workers (8 observed, 16.7 expected, SMR = 0.48, SMR = 0.21,0.95), who were also potentially exposed to pesticides (data not shown).

Table 6 presents SMRs for selected causes of death among men employed as lawn applicators by age hired and duration of employment. The age and duration categories were based on the distribution of the cohort without prior examination of the risk estimates. Two NHL cases were employed three or more years (SMR = 7.11, CI = 1.78, 28.42). No other cause of death was significantly elevated among the lawn applicators in the analysis of groups by age hired or duration of employment.

In other occupational groups within the cohort, there were no significant excesses or deficits for all causes combined or for specific causes of death (data not shown) except for significantly decreased mortality from accidents (SMR = 0.34, CI = 0.09,0.87), notably motor vehicle accidents (SMR = 0.25, CI = 0.03,0.89) among telemarketers, customer service, and collection employees.

The characteristics, job titles, and potential pesticide exposures of all subjects who died of bladder cancer, NHL, or other lymphatic or hematopoietic malignancies are presented in Table 7. Two of the three bladder cancer cases were part-time workers with little or no potential for expo-

TABLE 6

Observed Numbers of Deaths, Standardized Mortality Ratios (SMR), and 95% Confidence Intervals (95% CI) for Selected Causes of Death Among Male Lawn Applicators, by Age Hired and Duration of Employment, Adjusted by Race, Age, and Calendar Year

	All Causes			All Cancers			Non-Hodgkin's Lymphoma			Diseases of the Circulatory System			Cirrhosis			External Causes			Motor Vehicle Accident			Suicide		
Factor	***n***	**SMR**	**95% CI**	***n***	**SMR**	**95% CI**	***n***	**SMR**	**95% CI**	***n***	**SMR**	**95% CI**	***n***	**SMR**	**95% CI**	***n***	**SMR**	**95% CI**	***n***	**SMR**	**95% CI**	***n***	**SMR**	**95% CI**
Lawn applicators	165	0.69	0.59, 0.80	13	0.61	0.33, 1.05	3	1.63	0.33, 4.77	13	0.50	0.27, 0.86	5	1.02	0.33, 2.39	108	0.76	0.63, 0.92	42	0.78	0.56, 1.06	41	1.26	0.91, 1.71
Age hired																								
<26	96	0.64	0.52, 0.79	3	0.31	0.06, 0.90	1	0.99	0.01, 5.49	1	0.11	0.00, 0.62	3	1.68	0.34, 4.91	79	0.77	0.61, 0.96	33	0.80	0.55, 1.12	28	1.23	0.82, 1.78
26+	69	0.76	0.59, 0.96	10	0.87	0.42, 1.60	2	2.43	0.27, 8.76	12	0.71	0.37, 1.25	2	0.65	0.07, 2.33	29	0.75	0.50, 1.07	9	0.73	0.33, 1.38	13	1.34	0.71, 2.30
Duration of employment*																								
<1 year	136	0.81	0.68, 0.95	9	0.62	0.32, 1.20	1	0.75	0.11, 5.29	5	0.29	0.12, 0.70	3	0.97	0.31, 3.01	94	0.87	0.71, 1.07	37	0.88	0.64, 1.22	33	1.38	0.98, 1.94
1–2.9 years	20	0.51	0.33, 0.79	1	0.24	0.03, 1.74	0	—		4	0.80	0.30, 2.13	2	1.97	0.49, 7.88	9	0.40	0.21, 0.77	2	0.25	0.07, 1.00	6	1.11	0.50, 2.47
3+ years	13	0.52	0.30, 0.89	3	0.91	0.29, 2.83	2	7.11	1.78, 28.42	4	0.89	0.33, 2.36	0	—		5	0.42	0.18, 1.01	3	0.77	0.25, 2.38	2	0.66	0.16, 2.63

* Four cases with unknown cause of death included in the "all causes" AMFIT duration analyses.

TABLE 7
Characteristics of Current or Former ChemLawn Employees Who Died of Bladder Cancer or a Lymphatic or Hematopoietic Malignancy, 1969–1990

Cancer	Race/ Gender	Age Hired	Duration of Employment	Age at Death	ChemLawn Job	Pesticides Known To Be in Use at Branch When Subject Was Employed as Applicator
Bladder	WM	57	0.5 years	64.7	Telemarketing coordinator (part time)	
Bladder	WF	65	0.4 years	72.8	Secretary (part time)	
Bladder	WF	26	3.9 years	31.2	Lawn applicator (full time)	2,4-D, bensulide, chlorpyrifos, DCPA, dicamba, mecoprop
Non-Hodgkin's lymphoma	WM	26	3.0 years	32.6	Lawn applicator (full time)	2,4-D, benefin, bensulide, chlorpyrifos, DCPA, diazinon, dicamba, iron sulphate, mecoprop, pendamethalin, triclopyr
Non-Hodgkin's lymphoma	WM	32	0.6 years	35.6	Lawn truck helper (part time)	2,4-D, chlorpyrifos, DCPA, dicamba, dichlorprop, iron sulphate, MCPA, mecoprop, pendimethaline
Non-Hodgkin's lymphoma	WM	18	6.0 years	24.9	Lawn applicator, then assistant branch manager (full time)	2,4-D, aspon, atrazine, bensulide, chlorpyrifos, DCPA, dicamba, mecoprop, pronamide, trichlorfon
Non-Hodgkin's lymphoma	WF	36	0.4 years	37.8	Hold caller/collections (part time)	
Hodgkin's disease	WF	26	0.4 years	32.3	Computer clerk (part time)	
Leukemia	WM	25	1.1 years	32.8	Tree and shrub helper (part time), Tree and shrub applicator (full time)	Acephate, benomyl, carbaryl, diazinon, dicofol, Super W Oil
Leukemia	WM	26	0.1 years	32.5	Trainee (part time)	2,4-D, bensulide, chlorpyrifos, dicamba, isofenphos, mecoprop
Leukemia	WF	39	14.7 years	57.4	Secretary, office manager	

sure to pesticides. One bladder cancer case occurred in a female lawn applicator. Three of the four NHL cases were men employed in lawn application, all of whom had potential exposure to 2,4-D, chlorpyrifos, DCPA, dicamba, and mecoprop.

Discussion

This retrospective cohort mortality study of ChemLawn employees was based on a large population of 32,600 subjects, with excellent follow-up (99%) and detailed pesticide use data for many branch offices and years. The cohort, however, was quite young, with relatively short durations of employment and follow-up. The median age and year hired were 23 years and 1984, respectively. Approximately two-thirds (66%) of the employees worked for less than one year, with 77% less than two years. The median length of employment was 0.5 years, while the median length of follow-up was 6.8 years. Sixty-one percent of the person-years were accrued at ages under 30, and only 2% were accrued at age 50 or older. Few study subjects reached the ages at which cancer and death are most likely to occur.

Since special interest focused on the risk of NHL in this study population, it is noteworthy that the average age of diagnosis in three case-control studies of NHL conducted by NCI was 64.3 years. Between 25–29 and 65–69 years of age, there is a 24-fold increase in the mortality rate for NHL.[61] Therefore, the young age of the study population limits the power of the current analysis to evaluate the risk of NHL and many other tumors that increase with age. In addition, the short follow-up was also a limiting factor, since carcinogenic risks typically do not become apparent until 20 or more years after initial exposure.

The ChemLawn cohort had significantly lower than expected mortality for all causes of death combined, arteriosclerotic heart disease, symptoms and ill-defined conditions, and accidents. The lower mortality for all causes and arteriosclerotic heart disease is typical of that experienced by employed groups in comparison with the general population, which includes people too sick to work.[62–64] This "healthy worker effect" tends to be the most pronounced in young cohorts, particularly when some degree of physical fitness is required for the job, as for ChemLawn applicators. The healthy worker effect diminishes as time passes.

In our study, bladder cancer mortality was significantly increased, based on three deaths. Although excess bladder cancer has been reported in applicators handling the rodenticide ANTU[65] and in the first,[66] but not subsequent,[9] follow-up of another cohort of pesticide applicators, it seems unlikely that this excess was due to pesticide exposure. Although one bladder cancer case was a woman employed as a lawn applicator, the other two cases had no direct contact with pesticides in their part-time ChemLawn jobs.

There were four deaths due to NHL among the cohort. Three of the NHL deaths occurred among men employed in lawn application (SMR = 1.63), with two employed three or more years (SMR = 7.11). No other cause of death was significantly elevated among lawn applicators as a group or among those employed for three or more years. Ordinarily, one would not give much credence to the excess risk associated with duration, based on such small numbers. However, this was the only tumor with a duration effect in our study and the one with the strongest suspicion of a relation to herbicides based on previous epidemiologic studies of farmers, forestry workers, and gardeners.[6,12–16] The 1.63 overall risk for NHL among the applicators, although not statistically significant, was similar to the risks for NHL seen among farmers with a history of 2,4-D use in Kansas (odds ratio = 2.3)[12] and Nebraska (odds ratio = 1.5).[14] The significantly higher risk of 7.11 observed among longer duration applicators also resembles the higher risk observed among the most frequent users of herbicides in Kansas (odds ratio = 7.6)[12] and Nebraska (odds ratio = 3.3).[14]

If the relation between 2,4-D and NHL is real, one might expect higher risks among ChemLawn applicators than farmers, since the applicators apply pesticides between 90–120 days per year while farmers seldom apply more than 30 days per year. The young average age and short follow-up of the cohort, however, may have limited the power to detect an excess risk of NHL or other tumors. It is noteworthy that a significant excess of NHL (proportionate mortality ratio = 2.37) was observed in a survey of golf course superintendents, whose pesticide use in turf management resembles that of the ChemLawn cohort but who are older on average.[7]

Given the short follow-up to date in this study, the latent period (defined as the time from first exposure to diagnosis) for the NHL deaths among the cohort is also very short. In general, chemically induced NHL is thought to have an average latent period in the range of 15–20 years, similar to that of other solid tumors. In contrast, NHL associated with immunosuppression after renal transplantation begin to appear within a few months.[67,68] The short time from date hired to death from NHL observed in this cohort may: (1) indicate that the NHL deaths are not causally related to the subjects' pesticide exposures; (2) be for the first few deaths of a larger series that eventually will have an overall average of 15–20 years, or (3) indicate that the carcinogenic mechanism was related to immunosuppression, not classic chemical genotoxicity. Faustini et al[69] recently reported immunologic changes in farmers after short-term exposure to 2,4-D and MCPA. Significant reductions were observed in lymphocyte subsets including circulating helper (CD4) and suppressor T cells (CD8), CD8 dim, cytotoxic T lymphocytes (CTL), natural killer cells (NK), CD8 cells expressing the surface antigen HLA-DR (CD8-DR), and lymphocyte mitogen responses.

At this time, one cannot conclude that the NHL risk seen among ChemLawn workers is related to exposure to pesticides or to specific products such as 2,4-D. The applicators with NHL also had other herbicides and insecticides exposures in common, eg, chlorpyrifos, an organophosphate insecticide. Organophosphates have been linked to NHL previously.[14,18] As the number of deaths among the cohort increases over time, it may be possible to clarify risks and disentangle the effects of individual pesticides. Nonoccupational factors, however, seem unlikely explanations for the NHL excess seen in our study. Smoking, for example, is not a risk factor for NHL,[70] nor were most smoking-related causes of death elevated in this cohort. Immunosuppressive drugs[71] and hair dye use[72] have been linked to NHL but are extremely rare in young men. AIDS-related NHL must be a consideration in a cohort study of young men but would only confound our findings if the ChemLawn cohort was more likely to have AIDS-related NHL than the age-matched general population. There is no evidence that this is occurred, nor was AIDS reported on any of the NHL death certificates.

Summary

The ChemLawn cohort had low overall mortality, consistent with a healthy worker effect in this young employed population. Statistically significant excesses were observed for only two causes of death: bladder cancer among the cohort as a group and NHL among applicators employed for more than three years. The bladder cancer excess is unlikely to be related to pesticide exposure, since two of the three cases were part-time workers with no apparent contact with pesticides. The NHL excess in long-term employees was based on small numbers, but because of its consistency with previous studies, cannot be ignored. It is critical to continue follow-up as the cohort ages in the prospective component of this study, particularly for applicators with long duration of employment. In approximately five years, there would be sufficient statistical power to detect a twofold excess of NHL in the applicators as a group, and increased power to evaluate risks in the population employed for three or more years. Grouping all applicators together without consideration of type or amount of pesticides used may underestimate the risks associated with use of some specific pesticides. With more cases of NHL and other cancers, it will be possible to utilize the pesticide program data with a nested case-control approach to clarify risks overall and identify the individual pesticide exposures that may be involved. In the meantime, pesticide applicators should continue to take precautions to limit dermal exposure to pesticides as much as possible.

Acknowledgments

The author acknowledges Dr. Roger A. Yeary, TruGreen-ChemLawn, for his cooperation and support; Jimmie B. Vaught, formerly of Westat, Inc., and Patricia Lesho of Battelle/SRA for study management; and Bruce Ellis of Battelle for computer programming.

References

1. Blair A, Axelson O, Franklin C, et al. Carcinogenic effects of pesticides. In: Baker SR, Wilkinson CF, eds. *The Effects of Pesticides on Human Health. Advances in Modern Environmental Toxicology*, Vol. 18. Princeton, NJ: Princeton Scientific Publishing Co; 1990:201–260.
2. Zahm SH, Blair A. Carcinogenic risks from pesticides. In: Fortner JG, Rhoads JE, eds. *1992 Accomplishments in Cancer Research*. Philadelphia: J.B. Lippincott Co.; 1993:266–278.
3. Dich J, Zahm SH, Hanberg A, Adami H-O. Pesticides and cancer. *Cancer Causes Control*. 1997;8:420–423.
4. Blair A, Zahm SH. Cancer among farmers. *Occup Med*. 1991;6:335–354.
5. Pearce N, Reif JS. Epidemiologic studies of cancer in agricultural workers. *Am J Ind Med*. 1990;18:133–148.
6. Hansen ES, Hasle H, Lander F. A cohort study of cancer incidence among Danish gardeners. *Am J Ind Med*. 1992;21:651–660.
7. Kross BC, Burmeister LF, Ogilvie LK, Fuortes LJ, Fu CM. Proportionate mortality study of golf course superintendents. *Am J Ind Med*. 1996;29:501–506.
8. Figa-Talamanca I, Mearelli I, Valente P, Bascherini S. Cancer mortality in a cohort of rural licensed pesticide users in the province of Rome. *Int J Epidemiol*. 1993;22:579–583.
9. Pesatori AC, Sontag JM, Lubin JH, Consonni D, Blair A. Cohort mortality and nested case-control study of lung cancer among structural pest control workers in Florida (United States). *Cancer Causes Control*. 1994;5:310–318.
10. MacMahon B, Monson RR, Wang HH, Zheng T. A second follow-up of mortality in a cohort of pesticide applicators. *J Occup Med*. 1988;30:429–432.
11. Figa-Talamanca I, Mearelli I, Valente P. Mortality in a cohort of pesticide applicators in an urban setting. *Int J Epidemiol*. 1993;22:674–676.
12. Hoar SK, Blair A, Holmes FF, et al. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. *JAMA*. 1986;256:1141–1147.
13. Hardell L, Eriksson M, Lenner P, Lundgren E. Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study. *Br J Cancer*. 1981;43:169–176.
14. Zahm SH, Weisenberger DD, Babbitt P, et al. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. *Epidemiology*. 1990;1:349–356.
15. Wigle DT, Semenciw RM, Wilkins K, et al. Mortality study of Canadian male farm operators: non-Hodgkin's lymphoma mortality and agricultural practices in Saskatchewan. *J Natl Cancer Inst*. 1990;82:575–582.
16. Smith JG, Christophers AJ. Phenoxy herbicides and chlorophenols: a case control study on soft tissue sarcoma and malignant lymphoma. *Br J Cancer*. 1992;65:442–448.
17. Pearce NE. Phenoxy herbicides and non-Hodgkin's lymphoma in New Zealand: frequency and duration of herbicide use. *Br J Ind Med*. 1989;46:143–144.
18. Cantor KP, Blair A, Everett G, et al. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Res*. 1992;52:2447–2455.
19. Cantor KP, Blair A, Brown LM, Burmeister LF, Everett G. Correspondence re: K.P. Cantor et al, Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Res*. 1993;53:2421.
20. Woods JS, Polissar L, Severson RK, Heuser LS, Kulander BG. Soft tissue sarcoma and non-Hodgkin's lymphoma in relation to phenoxy herbicide and chlorophenol exposure in western Washington. *J Natl Cancer Inst*. 1987;78:899–910.
21. Woods JS. Non-Hodgkin's lymphoma among phenoxy herbicide-exposed farm workers in western Washington State. *Chemosphere*. 1989;18:401–406.
22. Coggon D, Pannett B, Winter P. Mortality and incidence of cancer at four factories making phenoxy herbicides. *Br J Ind Med*. 1991;48:173–178.
23. Lynge E. Cancer in phenoxy herbicide manufacturing workers in Denmark, 1947–87: an update. *Cancer Causes Control*. 1993;4:261–272.
24. Bloeman LJ, Mandel JS, Bond GG, Pollock AF, Vitek RP, Cook RR. An update of mortality among chemical workers potentially exposed to the herbicide 2,4-dichlorophenoxyacetic acid and its derivatives. *J Occup Med*. 1993;35:1208–1212.
25. Blair A, Zahm SH. Overinterpretation of small numbers in the Dow 2,4-D cohort study. *J Occup Environ Med*. 1995;37:126.
26. Hardell L. Soft-tissue sarcomas and exposure to phenoxy acids: a clinical observation. *Lakartidningen*. 1977;74:2753.
27. Hardell L, Sandstrom A. Case-control study: soft tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. *Br J Cancer*. 1979;39:711–717.
28. Eriksson M, Hardell L, Berg NO, Moller T, Axelson O. Soft tissue sarcomas and exposure to chemical substances: a case-referent study. *Br J Ind Med*. 1981;38:27–33.
29. Eriksson M, Hardell L, Adami H-O. Exposure to dioxins as a risk factor for soft tissue sarcoma: a population-based case-control study. *J Natl Cancer Inst*. 1990;82:486–490.
30. Hardell L, Eriksson M. The association between soft tissue sarcomas and exposure to phenoxyacetic acids: a new case-referent study. *Cancer*. 1988;62:652–656.
31. Vineis P, Terracini B, Ciccone G, et al. Phenoxy herbicides and soft-tissue sarcomas in female rice weeders: a population-based case-referent study. *Scand J Work Environ Health*. 1987;13:9–17.
32. Ott MG, Olson RA, Cook RR, Bond GG. Cohort mortality study of chemical workers with potential exposures to the higher chlorinated dioxins. *J Occup Med*. 1987;29:422–429.
33. Coggon D, Pannett B, Winter PD, Acheson ED, Bonsall J. Mortality of workers exposed to 2-methyl-4-chlorophenoxyacetic acid. *Scand J Work Environ Health*. 1986;12:448–454.
34. Fingerhut MA, Halperin WE, Marlow DA, et al. Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *N Engl J Med*. 1991;324:212–218.
35. Saracci R, Kogevinas M, Bertazzi PA, et al. Cancer mortality in workers exposed to chlorophenoxy herbicides and chlorophenols. *Lancet*. 1991;338:1027–1032.
36. Morrison H, Savitz D, Semenciw R, et al. Farming and prostate cancer mortality. *Am J Epidemiol*. 1993;137:270–280.
37. Munro IC, Carlo GL, Orr JC, et al. A comprehensive integrated review and evaluation of the scientific evidence relating to the safety of the herbicide 2,4-D. *J Am Coll Toxicol*. 1992;11:559, 561–664.
38. Environmental Protection Agency. *An*

SAB report: Assessment of Potential 2,4-D Carcinogenicity—Review of the Epidemiological and Other Data on Potential Carcinogenicity of 2,4-D by the SAB/SAP Joint Committee. [EPA-SAB-EHC-94-005.] Washington, DC: Environmental Protection Agency; March 1994.

39. Mustonen R, Kangras J, Vuojolahti P, Linnainmaa K. Effect of phenoxyacetic acids on the induction of chromosome aberrations in vitro and in vivo. *Mutagenesis.* 1986;1:241–255.
40. El-Zoka TA, McKenzie WH. Cytological effects of the herbicides 2,4-D and 2,4,5-T on human peripheral lymphocytes exposed in vitro. *Am J Hum Genet.* 1980;32:154A.
41. Turkala TE, Jalal SM. Increased rates of sister chromatid exchanges induced by the herbicide 2,4-D. *J Hered.* 1985;76: 213–214.
42. Korte C, Jalal SM. 2,4-D-induced clastogenicity and elevated rates of sister chromatid exchange in cultured human lymphocytes. *J Hered.* 1982;73:224–226.
43. Adhikari N, Grover IS. Genotoxic effects of some systemic pesticides: in vivo chromosomal aberrations in bone marrow cells in rats. *Environ Mol Mutagen.* 1988; 12:235–242.
44. Ibrahim M, Bond GG, Burke TA, et al. Weight of the evidence on the human carcinogenicity of 2,4-D. *Environ Health Perspect.* 1991;96:213–222.
45. Hazelton Laboratories. *Combined Toxicity and Oncogenicity Study in Rats, 2,4-Dichlorophenoxyacetic Acid (2,4-D): Final Report*, vol. 1. [Prepared for the Industry Task Force on 2,4-D Research Data.] Vienna, VA: Hazelton Laboratories America Inc.; 1986.
46. Hazelton Laboratories. *Oncogenicity Study in Mice with 2,4-Dichlorophenoxyacetic Acid (2,4-D): Final Report*, vol. 1. [Prepared for the Industry Task Force on 2,4-D Research Data.] Vienna, VA: Hazelton Laboratories America, Inc.; 1987.
47. Sott WT, Johnson KA, Gilbert KS, Ormand JR, Battjes JE. *2,4-Dichlorophenoxyacetic Acid: Dietary Oncogenicity Study in Male B6C3F1 Mice—Two-Year Final Report.* [Study ID: K-002372–063 M, EPA MRID No. 43879801.] Midland, MI: The Toxicology Research Laboratory, Dow Chemical Co.; November 16, 1995.
48. Sott WT, Johnson KA, Gilbert KS, Ormand JR, Battjes JE. *2,4-Dichlorophenoxyacetic Acid: Dietary Oncogenicity Study in B6C3F1 Mice: Two-Year Final Report.* [Study ID: K-002372–063F, EPA MRID No. 43597201.] Midland, MI: The Toxicology Research Laboratory, Dow Chemical Co.; March 10, 1995.
49. Jeffries TK, Yano BL, Ormand JR, Battjes JE. *2,4-Dichlorophenoxyacetic Acid Chronic Toxicity/Oncogenicity Study in Fischer 344 Rats: Final Report.* [Study ID: K-002372–064. EPA MRID No. 43612001.] Midland, MI: The Toxicology Research Laboratory, Dow Chemical Co.; March 28, 1995.
50. Linz DH, Suskind RR, Lockey JE, et al. Health status of pesticide applicators with attention to the peripheral nervous system. *J Agromed.* 1994;1:23–42.
51. Leonard JA, Yeary RA. Exposure of workers using hand-held equipment during urban application of pesticides to trees and ornamental shrubs. *Am Ind Hyg Assoc J.* 1990;51:605–609.
52. Yeary RA, Eaton J, Gilmore E, North B, Singell J. A multiyear study of blood cholinesterase activity in urban pesticide applicators. *J Toxicol Environ Health.* 1993;39:11–25.
53. Yeary RA, Leonard JA. Measurement of pesticides in air during application to lawns, trees and shrubs in urban environments. In: Racke KD, Leslie AR, eds. *Pesticides in Urban Environments: Fate and Significance.* [American Chemical Society Symposium Series.] Washington, DC: American Chemical Society; 1993; 522:275–281.
54. Yeary RA. Urinary excretion of 2,4-D in commercial lawn specialists. *Appl Ind Hyg.* 1986;3:119–121.
55. Monson RR. Analysis of relative survival and proportional mortality. *Comput Biomed Res.* 1974;7:325–32.
56. Boice JD Jr, Pickle L, Thomas TL, Helde TT Jr. *O/E System: Observed versus Expected Events: Users' Guide.* Bethesda, MD: National Cancer Institute; 1991.
57. Liddell FDK. Simple exact analysis of the standardized mortality ratio. *J Epidemiol Community Heatlh.* 1984;38:85–88.
58. Preston DL, Lubin JH, Pierce DA. *EPICURE: Program for Regression Analyses of Epidemiologic Data Including: AMFIT, PECAN, G'MBO, PEANUTS, and DATAB, a Transformation and Person-Year Tabulation Utility.* Seattle, WA: HiroSoft International Corp.; 1989.
59. Breslow NE, Day NE. *Statistical Methods in Cancer Research: The Design and Analysis of Cohort Studies*, vol. II. [IARC Scientific Pub 82.] Lyon: IARC; 1987:113–114, 120–159.
60. Boice JD Jr, Lubin JH, Preston DL. *EPITOME: Epidemiologic Analysis with a Personal Computer.* [NIH Pub. No. 91–3180.] Bethesda, MD: US Department of Health and Human Services, Public Health Service, National Institutes of Health; 1991.
61. Ries LAG, Miller BA, Hankey BF, Kosary CL, Harras A, Edwards BK. *SEER Cancer Statistics Review, 1973–1991: Tables and Graphs, National Cancer Institute.* [NIH Pub No 94–2789.] Bethesda, MD: National Institutes of Health; 1994:315.
62. McMichael AJ, Haynes SG, Tyroler HA. Observations on the evaluation of occupational mortality data. *J Occup Med.* 1975;17:128–131.
63. Fox AJ, Collier PF. Low mortality rates in industrial cohort studies due to selection for work and survival in the industry. *Br J Prev Soc Med.* 1976;30:225–230.
64. Monson RR. Observations on the healthy worker effect. *J Occup Med.* 1986;28: 425–433.
65. Davies JM, Thomas HF, Manson D. Bladder tumours among rodent operatives handling ANTU. *BMJ.* 1982;285: 927–931.
66. Wang HH, MacMahon B. Mortality of pesticide applicators. *J Occup Med.* 1979;21:741–744.
67. Kinlen LJ, Sheil AGR, Peto J, Doll R. A collaborative UK-Australasian study of cancer in patients treated with immunosuppressive drugs. *BMJ.* 1979;2:1461–1466.
68. Hoover R, Fraumeni JF Jr. Risk of cancer in renal-transplant recipients. *Lancet.* 1973;ii:55–57.
69. Faustini A, Settimi L, Pacifici R, et al. Immunological changes among farmers exposed to phenoxy herbicides: preliminary observations. *Occup Environ Med.* 1996;53:583–585.
70. Zahm SH, Weisenburger DD, Holmes FF, Cantor KP, Blair A. Tobacco and non-Hodgkin's lymphoma: combined analysis of three case-control studies. *Cancer Cause Control.* 1997;8:159–166.
71. Kinlen L. Immunosuppressive therapy and acquired immunological disorders. *Cancer Res.* 1992;(Suppl)52:5474s–5476s.
72. Zahm SH, Weisenburger DD, Babbitt PA, et al. Use of hair coloring products and the risk of lymphoma, multiple myeloma, and chronic lymphocytic leukemia. *Am J Public Health.* 1992;82:990–997.